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杨晓, 军事科学院军事医学研究院研究员。带领研究团队在国内率先建立小鼠条件性基因敲除技术体系, 系统地研究了TGF- β /Smad、PTEN/Akt等重要信号通路维持组织稳态的生理功能, 揭示了这些信号通路失调导致心脑血管疾病和肿瘤发生的因果联系和新机制。在*Cell Stem Cell*、*Developmental Cell*等专业杂志发表研究论文和综述200余篇, 引用超过24 280次, H指数81, 连续12年(2014—2025年)入选中国生物学领域高被引学者。作为第一完成人荣获2012年国家自然科学奖二等奖。2000年获得国家杰出青年科学基金资助, 2006年入选新世纪百千万人才工程国家级人选, 2013年被遴选为“万人计划”首批科技创新领军人才。曾经荣获第二十五届吴阶平-保罗·杨森医学药学奖、第十届中国青年科技奖、第三届中国青年女科学家奖、第九届求是杰出青年奖。现任*Military Medical Research*副主编, *International Journal of Biological Sciences*执行编辑, *Journal of Biological Chemistry*、《生命科学》、《中国细胞生物学学报》、《生物物理与生物化学进展》等杂志编委。

脑血管功能障碍驱动中枢神经系统疾病的机制

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摘要: 长期以来, 脑血管功能障碍被视为中枢神经系统疾病的继发或伴随现象。然而, 近年来的研究表明, 脑血管功能障碍在中枢神经系统疾病发生发展过程中具有关键的驱动作用。脑血管功能障碍如血流动力学紊乱、血脑屏障破坏、转运与清除功能受损以及血管旁分泌信号紊乱, 可通过破坏微环境稳态、神经血管通讯及诱发神经免疫炎症级联反应等, 促进多种中枢神经系统疾病的病理进程。本文系统总结脑血管功能在中枢神经系统生理与病理过程中的关键作用, 并结合多组学及影像学等技术进展, 探讨靶向脑血管的中枢神经系统疾病精准干预策略。

关键词: 脑血管异常; 中枢神经系统疾病; 神经血管单元

中图分类号: Q426; R743; R749.1

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Mechanisms underlying cerebrovascular dysfunction in driving central nervous system diseases

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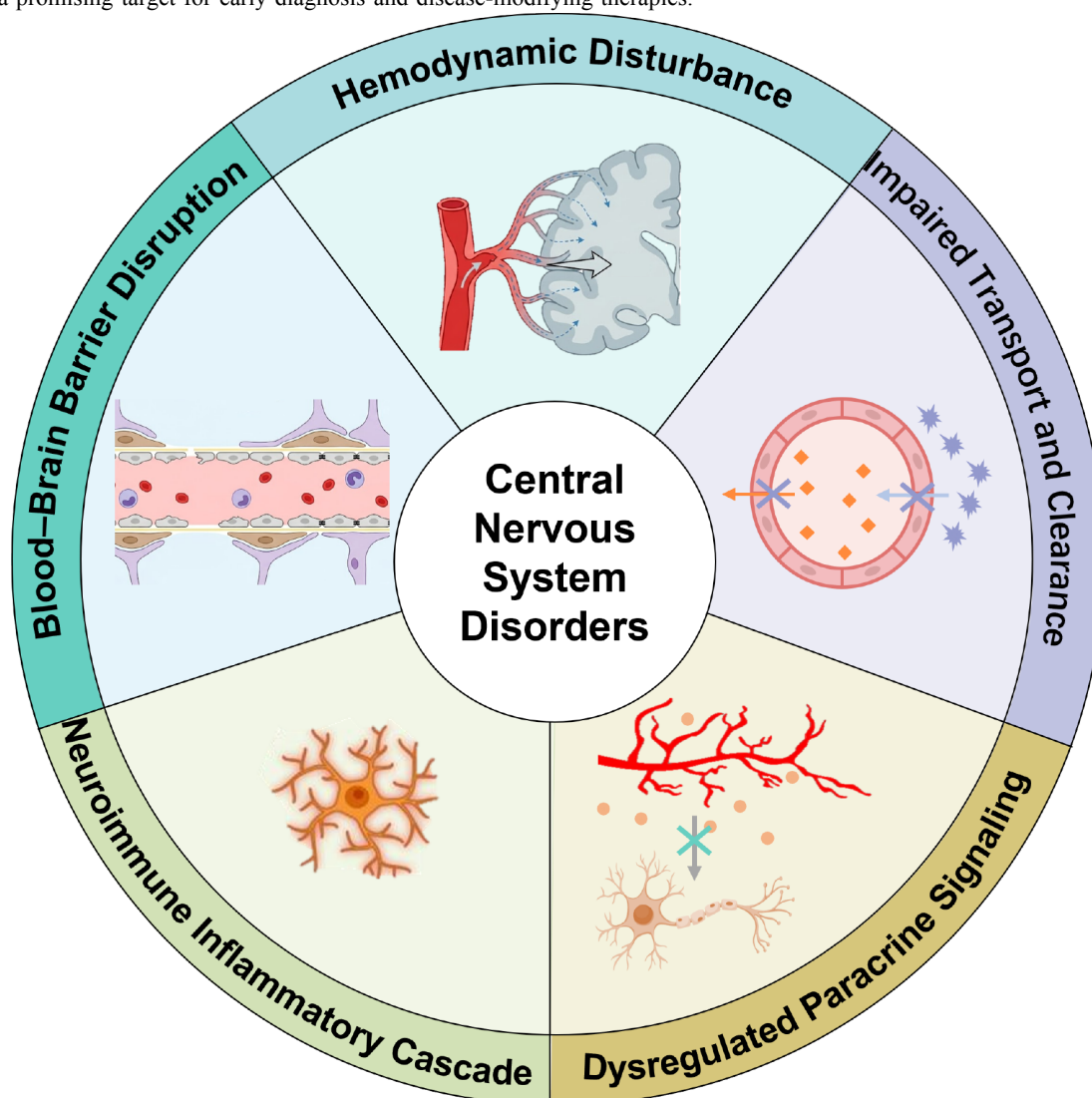
Abstract: Cerebrovascular dysfunction has long been regarded as a secondary or accompanying phenomenon in central nervous system (CNS) diseases. However, accumulating evidence from clinical, genetic, and experimental studies now indicates that vascular abnormalities actively contribute to the initiation and progression of a wide spectrum of CNS disorders. Cerebrovascular dysfunction, including cerebral hypoperfusion, disruption of the blood-brain barrier (BBB), impaired transport and clearance across the cerebrovascular interface, and dysregulated vascular paracrine signaling, can profoundly

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disturb neural microenvironmental homeostasis, compromise neurovascular communication, and trigger maladaptive neuroimmune and inflammatory cascades. These processes collectively accelerate neuronal dysfunction, compromise synaptic homeostasis, and drive neurodegeneration. This review systematically summarizes the essential physiological roles of the cerebrovasculature within the neurovascular unit (NVU), highlighting its contributions to neural development and the maintenance of CNS microenvironmental homeostasis through tightly regulated BBB transport of nutrients and metabolites, activity-dependent neurovascular coupling, and perivascular glymphatic clearance of metabolic waste. We then explore the pathological mechanisms by which cerebrovascular dysfunction drives CNS disease across five core dimensions: hemodynamic disturbances, which trigger neuronal energy crises, ionic imbalances, and excitotoxicity; BBB disruption, which permits the infiltration of neurotoxic plasma proteins (e.g., fibrinogen, thrombin) and peripheral immune cells; dysfunction of transport and clearance systems, leading to the accumulation of metabolic waste and pathogenic proteins such as amyloid- β and Tau; aberrant vascular paracrine signaling, which disrupts the intercellular crosstalk essential for neural development, synaptic plasticity, and inflammatory regulation; and neuroimmune inflammation, wherein vascular defects initiate self-perpetuating cascades that accelerate neuronal death. Finally, we highlight the translational potential of the cerebrovasculature as both a gateway for systemic interventions and an early indicator of CNS pathology. In the initial stages of disease, high-resolution vascular imaging can reveal subtle vascular abnormalities, while spatial multi-omics approaches map cerebrovascular heterogeneity to uncover actionable therapeutic targets. These macro- and micro-scale insights provide the basis for emerging precision medicine strategies, from imaging-guided patient stratification to combinatorial interventions aimed at restoring NVU integrity. Collectively, this review positions the cerebrovasculature as a key driver of CNS pathology and a promising target for early diagnosis and disease-modifying therapies.



Key words: cerebrovascular dysfunction; central nervous system disease; neurovascular unit

脑血管病与其他中枢神经系统(central nervous system, CNS)疾病是导致全球死亡与残疾的重要原因,给公共卫生系统带来了巨大挑战^[1]。临床研究数据显示,脑血管病与多种CNS疾病在流行病学层面存在显著相关性,并共享部分易感基因,两者常互为风险因素,提示二者之间具有密切的内在联系^[2-4]。受传统“神经元中心论”视角的影响,既往研究往往将脑血管功能障碍视为CNS疾病发生发展过程中的伴随或继发现象。例如,阿尔茨海默病(Alzheimer's disease, AD)经典的淀粉样蛋白级联假说通常将血管病变解释为 β -淀粉样蛋白($\text{amyloid-}\beta$, $\text{A}\beta$)沉积后的继发改变^[5];此外,早期的血流动力学观点往往将脑灌注不足理解为神经元丢失与脑萎缩后的被动适应,而未将其视为致病的始动因素^[6,7]。然而,近年累积的研究证据显示,脑血管功能障碍(包括血流动力学紊乱、血脑屏障(blood-brain barrier, BBB)渗漏、转运与清除功能障碍及旁分泌信号失调等)通常先于神经系统症状出现,提示其可能作为CNS疾病发生的早期驱动因素^[3,8-10]。因此,系统阐释脑血管生理功能并揭示其异常驱动CNS病理的关键机制,对于突破当前CNS疾病治疗瓶颈具有重要的理论和临床意义。本文基于最新的研究进展,首先概述脑血管在CNS中的关键生理作用,随后深入探讨脑血管功能障碍介导的病理过程如何驱动CNS疾病的发生发展,最后结合多组学与影像学等前沿技术的最新进展,探讨靶向脑血管的CNS疾病精准干预策略,为脑血管病与CNS疾病的联合防治提供新的理论依据和治疗思路。

1 神经血管单元的组成

2001年,“神经血管单元(neurovascular unit, NVU)”概念的提出,标志着脑科学领域认知范式的转变:即脑血管系统不再被视为孤立静止的物质运输管道,而是被重新定义为积极参与CNS发育、稳态维持及功能调节的活性组成部分^[11]。NVU包括脑血管内皮细胞、周细胞或平滑肌细胞、星形胶质细胞终足、小胶质细胞和神经元等细胞组分,以及基底膜与细胞外基质等非细胞成分,这一多细胞复合体是CNS实现生理功能与代谢调控的基本单元^[12]。在结构上,大脑血管由单层极化的内皮细胞构成管腔,其外紧密环绕周细胞或平滑肌细胞,二者共同嵌入基底膜中,构成血管结构的基本单元;星形胶质细胞

的终足广泛覆盖于基底膜外侧,形成血管-实质界面的功能连接;小胶质细胞以动态接触的方式分布于血管壁周围;神经元末梢则与这一复合界面建立直接的结构性连接(图1)。这些组分共同构成一个能动态响应神经活动、精确调控局部微环境的多细胞功能网络^[12]。

1.1 内皮细胞

脑血管内皮细胞是NVU的核心结构组分,位于脑血管管腔内壁,充当介导外周循环与脑实质进行物质与信息交换的功能界面。与外周血管内皮细胞的相对高通透性不同,脑血管内皮细胞通过表达高水平的紧密连接蛋白,有效封闭细胞旁通路,形成限制血源性物质非特异性进入脑内的物理屏障^[13]。同时,脑血管内皮细胞依靠其高度特化的转运系统精准介导营养物质的脑内转运及代谢废物的清除,为神经元与胶质细胞的功能稳态构建适宜微环境^[13]。此外,脑血管内皮细胞还具有活跃的分泌功能,通过释放各类活性因子与NVU中其他细胞组分共同构成动态的旁分泌调控网络。该网络不仅直接调控神经干细胞的增殖、迁移、成熟及神经元突触可塑性^[14-17],还能影响少突胶质前体细胞的发育与髓鞘形成过程^[18,19],并参与协调血管生成、BBB结构完整性及局部脑血流稳态^[20-22]。值得注意的是,2024年,单细胞转录组研究揭示内皮细胞沿“动脉-毛细血管-静脉”轴呈现显著的分子异质性,提示不同管径血管的内皮细胞在物质转运、免疫调控及血流调节中可能承担截然不同的功能^[23,24]。

1.2 周细胞

周细胞是紧密包绕于脑微血管内皮细胞外的多功能壁细胞,其形态与功能沿动静脉轴连续变化。在NVU中,周细胞可响应电刺激、神经递质及缺血等信号,通过其收缩机制动态调控毛细血管直径,介导局部血流与神经代谢的耦联^[25,26]。在血管生成与重塑中,周细胞与内皮细胞通过血管内皮生长因子(vascular endothelial growth factor, VEGF)/血管内皮生长因子受体(VEGFR)、血小板衍生生长因子-B(platelet-derived growth factor-B, PDGF-B)/血小板衍生生长因子受体- β (PDGFR- β)等信号通路相互调控^[21,27]。此外,周细胞还参与BBB结构与功能的维持,且其分子表型与功能的脑区特异性可能是导致BBB呈现区域异质性的重要原因^[28,29]。在CNS损伤后,部分周细胞可脱离血管壁并分化为成

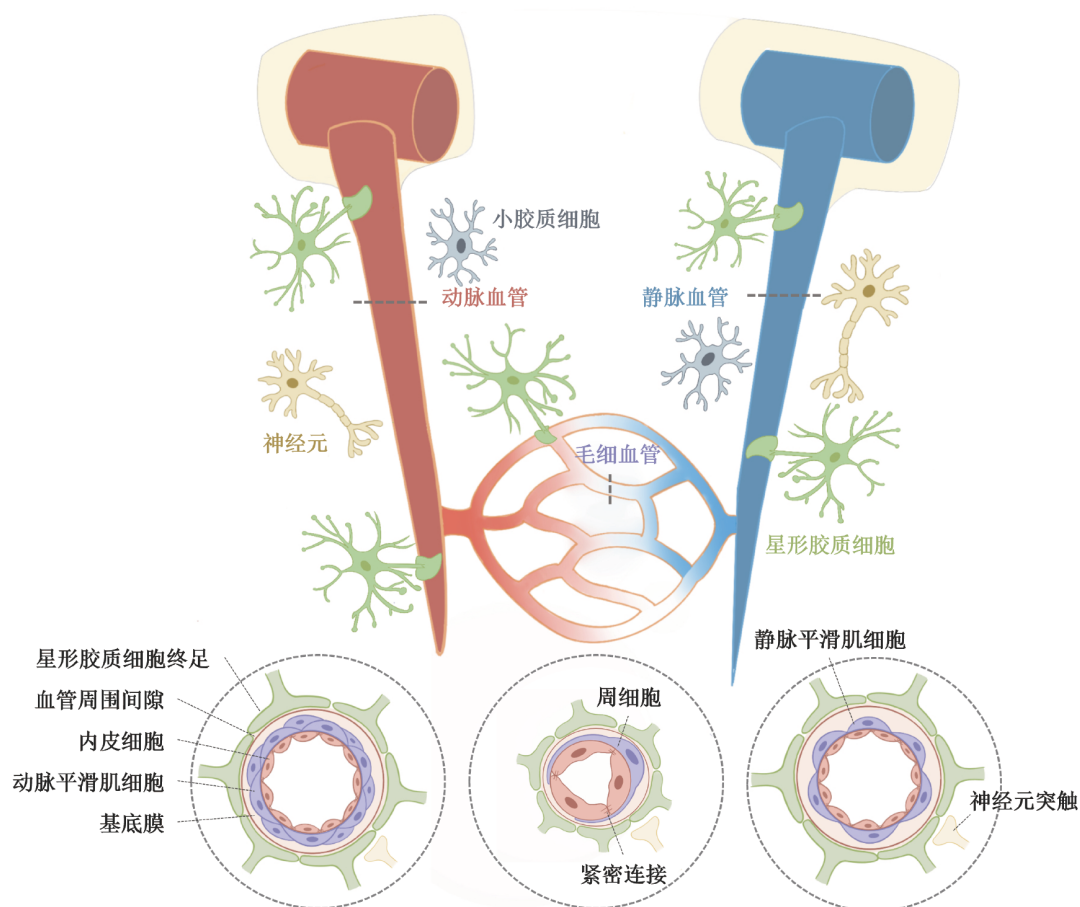


图1 不同血管段神经血管单元结构模式图

本图示意神经血管单元的结构组成。动脉与静脉通过毛细血管网相连,共同构成脑微循环系统。血管壁由内皮细胞连续形成,细胞间通过紧密连接构成血脑屏障的结构基础。动脉壁具有发达的平滑肌细胞层,而静脉的平滑肌层相对较薄;毛细血管壁则分布有周细胞。血管外侧被星形胶质细胞终足包裹,周围分布有神经元和小胶质细胞等,共同构成神经血管单元。

Figure 1 Structural schematic of the NVU in different vascular segments

This schematic illustrates the structural organization of the NVU. Arteries and veins are connected via a capillary network, forming the cerebral microcirculation. The vessel wall is continuously lined by endothelial cells, which are interconnected by tight junctions that constitute the structural basis of the BBB. The arterial wall contains a well-developed smooth muscle cell layer, whereas the venous smooth muscle layer is comparatively thin. Pericytes are distributed along the capillary wall. The outer surface of the vessels is ensheathed by astrocytic endfeet, and the surrounding parenchyma contains neurons and microglial cells, among other cellular components, collectively comprising the NVU.

纤维细胞样表型,通过分泌胶原蛋白等细胞外基质成分参与纤维化瘢痕的形成^[30,31]。

1.3 星形胶质细胞

星形胶质细胞是CNS中分布最广泛的胶质细胞。在结构上,其突起末端形成的终足紧密包裹脑毛细血管,构成BBB的外层界面。该界面介导血管与脑实质之间的信号整合、物质交换与局部微环境稳态维持^[13]。在功能层面,星形胶质细胞能够感知并整合神经元活动信号,通过释放血管活性分子调节血管舒缩,从而将神经元活动与局部脑血流变化

耦联,以满足神经组织的代谢需求^[32,33]。在能量代谢方面,星形胶质细胞可摄取血源性葡萄糖并将其转化为乳酸,作为神经元的关键能量底物^[34]。此外,星形胶质细胞还在脑内稳态调控中发挥关键作用,其终足富集的水通道蛋白4(aquaporin 4, AQP4)参与脑内水分动态调节^[35]。同时,星形胶质细胞通过重摄取兴奋性神经递质(如谷氨酸)以及清除细胞外 K^+ ,维持突触微环境稳定并调控神经元兴奋性^[36,37]。在病理状态下,星形胶质细胞会发生反应性增生,但其形成的胶质瘢痕在限制损伤扩散的同

时也可能阻碍神经再生^[38]。

1.4 小胶质细胞

小胶质细胞是CNS的常驻巨噬细胞,利用其表面丰富的受体,持续感知并监视脑内微环境^[13]。生理状态下,小胶质细胞通过吞噬错误折叠蛋白、细胞碎片及死亡细胞等机制,参与维持脑内稳态^[39]。一旦识别病原相关分子模式(PAMPs)、损伤相关分子模式(DAMPs)或异常蛋白聚集物,小胶质细胞会迅速活化,启动形态和功能重编程^[39]。传统上,其活化状态被分为促炎(M1样)和抗炎/修复(M2样)两种类型:M1样表型在急性损伤期可有效清除病原体与死亡细胞,但持续活化可能加重组织损伤;M2样表型则主要介导炎症消退及组织重建,促进神经微环境恢复^[39]。然而,近年来的单细胞转录组学研究表明,小胶质细胞在发育与疾病中呈现高度转录异质性,其功能多样性远超传统的M1/M2框架,提示其活化谱系受到更加精细和动态的调控^[40,41]。在神经发育过程中,小胶质细胞通过突触修剪机制吞噬多余弱突触,直接参与神经环路的优化^[42]。此外,小胶质细胞还能利用嘌呤能受体P2Y₁₂与血管内皮细胞、壁细胞及星形胶质细胞建立物理接触,直接参与毛细血管直径与脑血流的动态调控^[43,44]。

2 脑血管系统的核心生理功能

哺乳动物大脑作为高度血管化的复杂器官,其脑血管网络与CNS在发育、结构及功能上密切相关且高度协同^[12]。作为NVU的调控枢纽,脑血管通过为神经元提供物理支架、旁分泌信号及重塑代谢微环境,参与神经系统的发育构建与功能维持。在稳态层面,脑血管系统通过维持BBB、介导神经血管耦合(neurovascular coupling, NVC)以及驱动类淋巴清除等机制,保障中枢神经系统内环境的稳态。

2.1 脑血管调控中枢神经系统发育

脑血管系统与CNS的发育高度协同,脑血管通过重塑代谢微环境、引导神经元迁移及释放旁分泌信号共同调控CNS的构建。在代谢层面,血管浸润重塑局部微环境,促使神经前体细胞由依赖糖酵解的缺氧增殖状态,转向依赖氧化磷酸化的分化状态,从而启动细胞命运转变^[45,46]。在神经元迁移过程中,血管不仅充当物理支架,还通过建立 γ -氨基丁酸(γ -aminobutyric acid, GABA)等化学梯度,指引其在皮层中精确定位^[16,47]。除上述物理与代谢支撑外,

脑血管还作为一个活跃的信号枢纽,在不同发育阶段分泌VEGF、PDGF、胰岛素样生长因子-1(insulin-like growth factor-1, IGF-1)、脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)和信号素3G(semaphorin 3G, Sema3G)等因子,直接调控从神经发生、存活到突触回路组装的完整过程^[14,48-51]。

2.2 脑血管维持中枢神经系统稳态

2.2.1 血脑屏障维持内环境稳态

BBB是由脑微血管内皮细胞、周细胞及星形胶质细胞终足共同构成的多细胞复合体。其中,脑微血管内皮细胞是BBB的结构和功能基础,具有无窗孔结构、极低的囊泡转运水平及高度特化的细胞间连接等特征^[52]。紧密连接是屏障功能的关键结构,主要由闭合蛋白-5(Claudin-5)、咬合蛋白(Occludin)等跨膜蛋白经由闭锁小带蛋白(zonula occludens proteins, ZO)连接细胞骨架,有效封闭细胞旁间隙,限制溶质的自由扩散^[53]。黏附连接则位于基底膜侧,依赖血管内皮钙黏蛋白(vascular endothelial cadherin, VE-cadherin)与 α -连环蛋白(α -catenin)、 β -连环蛋白(β -catenin)及p120-连环蛋白(p120-catenin)等连环蛋白家族成员形成复合体,介导细胞间的机械锚定,从而增强细胞间黏附并维持紧密连接的完整性^[54]。

在严密的物理屏障基础之上,脑内皮细胞利用特化的转运系统实现必需物质的跨BBB运输。小分子物质的转运主要依赖溶质载体(solute carrier, SLC)与ATP结合盒转运体(ATP-binding cassette transporter, ABC)两大家族^[55]。SLC转运蛋白主要介导葡萄糖、氨基酸、维生素、阳离子及有机阴离子等物质的跨BBB转运,为CNS提供必需营养与信号分子^[56]。ABC转运体则作为主动外排泵,通过水解ATP供能,将内源性代谢废物及外源性毒素逆浓度梯度排出脑外,维系CNS微环境稳态^[57]。对于无法通过载体转运的大分子物质(如胰岛素、转铁蛋白),内皮细胞主要依赖受体介导的转胞吞作用进行运输,该过程中大分子与特异性受体结合后,由网格蛋白或小窝蛋白包被形成囊泡,从而完成跨内皮的定向转运^[58]。

除物理屏障作用外,BBB还能根据生理需求动态调节自身功能,以适应神经活动、昼夜节律、代谢状态及激素水平的变化^[52]。具体而言,神经元活动增强会提升局部代谢需求,进而通过调控BBB的转

运功能,增加必需营养物质的脑内供应^[59,60]。与此同时,BBB的功能也显著受到昼夜节律的调控,其多种关键转运蛋白及酶的表达呈现节律性波动,从而依赖时间调节物质的入脑与清除^[61,62]。代谢状态同样参与BBB功能调控,如禁食与进食转换可通过过氧化物酶体增殖物激活受体 δ (PPAR- δ)等信号通路调整能量底物供应效率与屏障紧密性^[63,64]。激素调控亦扮演关键角色,雌激素、睾酮和孕激素等可通过调节紧密连接蛋白表达及抑制炎症通路来动态调节BBB完整性^[65-67]。

2.2.2 神经血管耦合精准调控脑血流

NVC是精准调节局部脑血流以匹配神经元代谢需求的机制。当神经元活动增强导致耗能增加时,该机制通过整合代谢性及神经源性信号,动态调控血管舒缩,以维持局部的能量供需平衡^[12]。这一过程依赖于NVU内高度协同的信号网络。具体而言,神经元兴奋释放的谷氨酸可激活中间神经元和星形胶质细胞:中间神经元主要分泌一氧化氮(NO),而星形胶质细胞则通过钙信号通路释放 K^+ 及花生四烯酸代谢产物(如前列腺素)等,这些血管活性物质协同作用于血管壁细胞及内皮细胞,诱导血管舒张并迅速提升局部血流^[32,68]。研究还揭示了一种更为高效的“类突触式”调控模式:谷氨酸可经由神经元-小动脉平滑肌接头,直接作用于平滑肌表面的N-甲基-D-天冬氨酸受体(NMDAR)^[69]。在小鼠桶状皮层胡须刺激实验中,特异性敲除该受体导致感觉诱发性血流响应幅度下降约60%,证实了该通路在生理性充血中的关键作用^[69]。此外,由连接蛋白构成的内皮缝隙连接网络形成了长程信号传导通路,使舒张信号能沿内皮细胞快速传播^[70]。

2.2.3 类淋巴系统介导代谢废物清除

类淋巴系统是CNS维持内环境稳态的关键清除机制。该系统与脑血管高度耦联,不仅依托血管周围间隙构建了低阻力通道,更利用脑动脉搏动产生的流体动力,驱动脑脊液与脑组织间液的高效交换^[71]。这一过程始于脑脊液沿深穿小动脉间隙深入脑实质^[71]。随后,在星形胶质细胞终足AQP4极性分布的驱动下,脑脊液与组织间液发生跨膜交换并形成定向对流,将 $A\beta$ 、Tau蛋白等代谢废物从脑实质驱向静脉周围间隙,并经脑膜淋巴管引流至颈深部淋巴结^[36,72]。此外,类淋巴系统的清除效率受昼夜节律的显著调控。在休息期,脑组织间隙体积显

著扩大,由此引发的流体阻力降低促进了脑脊液进入脑实质^[73]。与此同时,AQP4极性分布的昼夜动态变化亦起到协同作用,使得小鼠在休息期的脑脊液流入及废物清除效率显著高于活动期^[74]。

3 脑血管功能障碍驱动中枢神经系统疾病的病理机制

在遗传变异、衰老、代谢紊乱及环境压力等因素的作用下,脑血管功能障碍往往成为CNS病理改变的起始环节^[6,75]。本节将从血流动力学紊乱、BBB渗漏、转运与清除功能障碍、旁分泌信号失调及神经炎症五个维度,系统阐述脑血管功能障碍驱动CNS疾病的机制。值得注意的是,这些病理过程并非孤立存在,而是相互交织、互为因果,共同构成驱动疾病发展的恶性网络。

3.1 血流动力学紊乱引发脑能量代谢危机

由于神经元自身缺乏糖原储备且代谢需求极高,其生存与功能完全依赖血液循环的持续供能。因此,当NVC失效或微循环停滞导致供能中断时,血管源性的功能障碍将迅速波及神经元,诱发其病理改变。临床研究已经证实,脑血流灌注不足是许多CNS疾病中的常见病理现象,在AD、血管性痴呆(vascular dementia, VaD)、帕金森病(Parkinson's disease, PD)、精神分裂症及抑郁症等疾病中尤为突出^[76-80]。

这种由血流动力学紊乱引发的能量危机首先表现为ATP耗竭,进而触发离子稳态失衡与兴奋性毒性。神经元消耗的能量绝大部分用于维持 Na^+/K^+ -ATP酶的运转以保持静息膜电位,而血流灌注不足导致的ATP合成锐减致使离子泵功能丧失及膜电位持续去极化^[81]。这种膜电位改变通过双重机制诱发严重的钙超载:一方面,去极化直接导致电压门控钙通道异常开放^[82];另一方面,去极化状态解除了NMDAR的 Mg^{2+} 阻滞,协同突触间隙积聚的高浓度谷氨酸,致使NMDAR被过度激活^[83]。这两类通道的协同开放介导 Ca^{2+} 爆发式内流,引发下游死亡信号级联反应,最终导致神经元坏死或凋亡^[84]。

与此同时,缺氧导致的无氧糖酵解代偿性增强会引起组织乳酸堆积与酸中毒,这种微环境的pH值下降会进一步激活酸敏感离子通道,介导 Na^+ 与 Ca^{2+} 的病理性内流,引发严重的胞内钙超载,最终加剧神经元损伤^[85]。

除了上述急性损伤,长期能量耗竭还会破坏蛋白质稳态。错误折叠蛋白(如 $A\beta$ 和Tau)的降解与自噬过程均为高度耗能过程,慢性低灌注引发的ATP匮乏会显著抑制泛素-蛋白酶体系统及自噬-溶酶体途径的活性,导致毒性蛋白在神经元内外的病理性沉积^[86,87]。

此外,为缓解代谢压力,神经元会主动抑制高耗能的突触传递,从而降低能量需求。这种适应性的“突触沉默”虽在短期内维持了细胞生存,却会损害信息传递功能,导致早期认知功能下降^[88]。若能量匮乏长期持续,这种功能性的抑制可进一步转变为结构性的突触回缩,最终造成神经网络连接的不可逆中断^[89]。

3.2 血脑屏障破坏介导神经毒性物质浸润

BBB完整性丧失是脑血管功能障碍的常见病理特征。临床研究证实,在AD、PD、多发性硬化(multiple sclerosis, MS)、脊髓小脑共济失调(spino cerebellar ataxia, SCA)等疾病中,均存在不同程度的BBB功能障碍^[90-93]。尤其在AD中, BBB渗漏甚至可早于认知衰退、神经元变性或脑萎缩等典型表现出现^[93,94],提示其在疾病早期扮演关键角色。此外, BBB功能障碍在精神类疾病中的致病效应也日益明确,例如慢性应激可直接诱导脑血管紧密连接丢失及通透性增加,这种血管源性的病理改变已被证实是驱动抑郁样行为发生的关键机制^[95,96]。

BBB完整性受损会使CNS直接暴露于多种血液来源的物质,进而通过不同机制引发神经损伤。其中,渗入的纤溶酶原被激活为纤溶酶后,可降解神经元附着的细胞外基质中的层粘连蛋白,导致其因失去支持而发生脱巢凋亡^[97]。同时,高浓度凝血酶能通过受体途径直接产生神经毒性并损害突触可塑性^[98]。纤维蛋白原则沉积于血管周围,不仅引发轴突回缩,还可作为强效促炎剂激活小胶质细胞^[99]。此外,普遍存在的红细胞外渗使得含铁蛋白(如血红蛋白)在血管周围积累,其在分解过程中释放游离铁并产生活性氧(ROS),导致神经元处于持续的氧化应激状态^[100]。另一方面,血浆白蛋白的渗漏会改变组织渗透压,引发严重的血管源性水肿,这种病理改变会物理性压迫微血管,进一步阻碍局部微循环与脑脊液流动,形成“缺氧-水肿”的恶性循环^[101]。

BBB的破坏标志着CNS免疫特权的崩塌。外周免疫细胞,包括先天免疫系统的巨噬细胞、中性粒细

胞,以及适应性免疫系统的T淋巴细胞与B淋巴细胞,可经破损的屏障浸润至脑实质^[102-104]。这种免疫细胞浸润会释放大量炎性细胞因子与趋化因子,形成慢性神经炎症,进一步损害神经元与胶质细胞。

3.3 血管介导的转运与清除功能障碍导致代谢失衡与废物蓄积

脑血管通过特异性的转运体与受体系统,精确介导营养物质入脑及代谢废物外排,是维持CNS微环境稳态的关键枢纽^[52]。当转运与清除功能发生障碍时,大脑不仅面临能量与合成底物供给不足的问题,还会因有害物质的滞留而暴露于持续的毒性应激之下,最终诱发或加速CNS疾病。

关键营养物质转运载体的表达或功能异常,可通过扰乱特定代谢通路,导致从神经发育障碍到神经退行性病变的一系列神经系统异常。例如,葡萄糖转运蛋白1(glucose transporter 1, GLUT1)若发生功能缺陷,会导致大脑能量供应不足,进而引发癫痫、认知障碍及小头畸形等神经系统异常^[105]。同样,在长链脂肪酸转运中起关键作用的含主要易化子超家族结构域蛋白2A(major facilitator superfamily domain-containing protein 2A, MFSD2A)一旦失活,不仅会损害BBB完整性,还会因二十二碳六烯酸(DHA)等必需脂肪酸的缺乏,导致神经发育缺陷,如小头畸形和智力障碍^[106]。此外,在PD中,脑内皮细胞L型氨基酸转运蛋白1(L-type amino acid transporter 1, LAT1)的表达常出现下调,限制了酪氨酸和色氨酸等进入脑内,影响多巴胺和血清素等递质的合成,从而加剧患者的运动障碍及情绪异常^[107]。

有害代谢产物与致病蛋白的清除障碍,是蛋白聚集性CNS疾病的重要病理机制。在AD中, $A\beta$ 的清除主要依赖脑内皮细胞表面的低密度脂蛋白受体相关蛋白1(low-density lipoprotein receptor-related protein 1, LRP1)^[108]。然而,在AD患者脑血管内皮细胞中,LRP1表达常显著下调,导致 $A\beta$ 外排效率降低,使其在脑内异常积累并形成老年斑;同时,累积的 $A\beta$ 又可进一步抑制LRP1功能,形成恶性循环^[109]。类似地,在PD中, α -突触核蛋白(α -Syn)的异常聚集是疾病进展的主要病理事件之一,其清除依赖于脑血管内皮细胞表面的P-糖蛋白(P-glycoprotein, P-gp)。当P-gp表达或功能受损时, α -Syn的持续积累会选择性损伤多巴胺能神经元,加速疾病进程^[110]。除上述致病蛋白外,代谢产物的

清除同样关键。例如,脑血管内皮细胞中磷酸酶和张力蛋白同源物(PTEN)的缺失会通过下调单羧酸转运蛋白1(monocarboxylate transporter 1,MCT1)影响乳酸跨BBB转运,造成脑内乳酸异常堆积,进而干扰成年海马神经发生及损害认知功能^[111]。此外,在AD及脑小血管病中,血管壁发生的病理性重构与硬化会导致其舒缩能力显著下降,损害脑内类淋巴系统的液体流动,导致毒性蛋白无法被有效清除而在脑中滞留^[112,113]。这种血管功能的下降往往发生于明显的蛋白沉积之前,提示其可能是神经退行性病变的早期驱动因素^[114]。

表1对血脑屏障关键转运体功能障碍驱动中枢神经系统疾病的病理机制进行了总结。

3.4 血管旁分泌信号失调致使细胞间通讯障碍

血管旁分泌信号紊乱可直接破坏NVU内的细胞间通讯与功能协同,并广泛参与多种神经系统病理过程。其中,参与神经系统发育调控的关键血管旁分泌信号一旦发生异常,往往会扰乱神经细胞的增殖、迁移及命运决定。例如,内皮细胞来源的VEGF缺失可阻断胚胎发育中后期脑室周围血管生成,并伴随神经元过度增殖和迁移紊乱,最终导致端脑结构严重畸形^[17]。同样,内皮来源的软骨中间层蛋白2(cartilage intermediate layer protein 2,CILP2)的缺失会干扰Wnt信号通路并改变神经前体细胞命运,使小鼠表现出类似孤独症的行为^[125]。

血管旁分泌信号异常还与突触功能障碍及神经环路稳态失衡密切相关。研究发现,AD患者脑内皮

细胞分泌的BDNF水平下降,与长时程增强(LTP)受损及认知衰退密切相关^[126]。此外,血管内皮分泌的Sema3G缺失会直接降低树突棘密度,损害海马依赖性记忆^[14],而血管生成素(angiopoietin,Ang)/酪氨酸激酶受体2(tyrosine kinase receptor 2,Tie2)信号轴的失调则导致小脑浦肯野细胞树突分支显著减少,进而破坏神经网络的整合功能^[127]。

血管旁分泌信号在神经炎症调控中同样发挥关键作用。正常情况下,血管内皮通过持续分泌转化生长因子- β (transforming growth factor-beta,TGF- β)等因子维持小胶质细胞的静息状态,而该抑炎信号的丧失将解除对胶质细胞的生理性抑制并引发神经炎症^[128]。

表2对脑血管旁分泌信号异常介导中枢神经系统疾病的病理机制进行了总结。

3.5 脑血管功能障碍诱发神经免疫炎症级联反应

神经免疫炎症是推动多种CNS疾病发生发展的核心病理机制。脑血管功能障碍通过血流动力学紊乱、BBB破坏、转运清除障碍及旁分泌信号失调,构成了激活中枢免疫反应的多重病理基础。

在病理环境的持续刺激下,过度活化的小胶质细胞持续释放多种促炎介质和氧化应激分子,直接造成神经元损伤。例如,肿瘤坏死因子- α (tumor necrosis factor-alpha,TNF- α)可通过激活死亡受体通路,启动半胱天冬酶(caspase)级联反应,最终诱导神经元凋亡^[144]。同时,高浓度的白细胞介素-1 β (interleukin-1 β ,IL-1 β)可增强NMDAR功能,加剧谷

表1 血脑屏障关键转运体功能障碍驱动中枢神经系统疾病的病理机制

Table 1 Pathological mechanisms of CNS diseases driven by dysfunction of key BBB transporters

载体名称	主要转运物质	病理机制	代表性疾病
GLUT1	葡萄糖	脑能量供给不足	GLUT1缺陷综合征、AD ^[105]
LAT1	大中性氨基酸	必需氨基酸摄入不足,影响蛋白合成与信号	孤独症、癫痫 ^[115,116]
MFSD2A	二十二碳六烯酸	必需脂肪酸摄入不足,影响膜结构与功能	小头畸形 ^[106]
OATP1C1、MCT8	甲状腺激素	脑内甲状腺激素信号不足	艾伦-赫恩登-达德利综合征 ^[117]
OCTN2	L-肉碱	脂肪酸进入线粒体受阻,能量代谢受损	原发性肉碱缺乏症 ^[118]
RAGE	A β 、晚期糖基化终末产物	介导外周A β 等毒性物质入脑,并引发炎症	AD ^[119,120]
LRP1	A β 、载脂蛋白E	脑内A β 清除至血液的效率下降	AD、脑血管淀粉样血管病 ^[119]
P-gp	A β 、多种药物及毒素	外排功能下降,导致毒性物质蓄积	AD、药物抵抗性癫痫 ^[121,122]
MCT1	乳酸、酮体	乳酸在脑内蓄积	认知功能受损 ^[111]
OCTs/OATs	有机阴/阳离子、神经递质代谢物	内源性废物或外源性毒素蓄积	尿毒症脑病、精神症状 ^[123,124]

注:OAT1C1(organic anion transporter 1C1,有机阴离子转运体1C1);MCT8(monocarboxylate transporter 8,单羧酸转运体8);OCTN2(organic cation/carnitine transporter 2,有机阳离子/肉碱转运体2);RAGE(receptor for advanced glycation end products,晚期糖基化终产物受体);OCTs(organic cation transporters,有机阳离子转运体家族);OATs(organic anion transporters,有机阴离子转运体家族)。

表2 脑血管旁分泌信号异常介导中枢神经系统疾病的病理机制

Table 2 Pathological mechanisms of CNS diseases mediated by abnormal cerebrovascular paracrine signaling

类别	分泌物质	主要来源	主要作用机制	病理后果
神经营养与修复	VEGF	内皮细胞	促进血管生成并增加血管通透性	发育期缺失:血管生成不足、神经迁移异常;病理期过高:BBB破坏与严重脑水肿 ^[17,95]
	BDNF	内皮细胞	激活TrkB受体,促进突触可塑性 与神经元存活	内皮来源BDNF减少;LTP受损、突触退化与认知功能下降 ^[51,126]
	IGF-1	内皮细胞	激活PI3K-Akt信号,支持神经元 代谢与存活	内皮IGF-1下降;神经元能量脆弱性增加,加速神经退行与认知衰退 ^[129,130]
炎症与免疫调节	IL-1 β 、IL-6、TNF- α	内皮细胞、周细胞	激活NF- κ B等炎症信号,放大免疫 反应	驱动慢性神经炎症,导致BBB破坏、突触损伤与神经退行 ^[131-134]
	CCL2	内皮细胞、周细胞	招募单核/巨噬细胞至病灶	促进免疫细胞入脑,加剧卒中、MS、AD 的炎症损伤 ^[135,136]
	TGF- β	内皮细胞、周细胞	抗炎、诱导ECM沉积与血管重塑	信号缺失:小胶质细胞异常激活;过度 表达:血管纤维化与脑淀粉样血管病 ^[128,137]
	CXCL1	内皮细胞	募集并激活免疫细胞,参与神经 免疫监视与炎症调节	过度表达:谷氨酸稳态失衡与突触兴奋 性异常,从而驱动癫痫发生 ^[138]
	CXCL12	内皮细胞	维持免疫细胞在血管周围定位, 限制入脑	信号破坏:免疫细胞异常穿越BBB,导 致慢性神经炎症 ^[139]
	Netrin-1	内皮细胞	维持内皮连接与抗炎表型	表达下降:BBB不稳定、炎症细胞入脑 增加 ^[140]
凝血与屏障功能	MMP-9	内皮细胞、周细胞	降解ECM与紧密连接蛋白	BBB破坏、脑水肿与出血,是卒中急性 期损伤关键介质 ^[141]
	tPA	内皮细胞	溶栓并参与细胞信号调控	外渗或过量:脑出血风险升高并产生神 经毒性 ^[142,143]
神经发育与可塑性调控	CILP2	内皮细胞	干扰Wnt/ β -catenin信号	内皮CILP2缺失:神经前体细胞命运异 常,出现孤独症 ^[125]
	GABA	内皮细胞	调控发育期神经元的迁移与精确 定位	内皮源性GABA信号缺失导致神经元 迁移异常,引发多动、焦虑、社交缺陷等 行为障碍 ^[16]
	Sema3G	内皮细胞	轴突导向与突触结构调控	缺失导致树突棘密度下降、突触可塑性 与记忆受损 ^[14]
	Ang1、Ang2	内皮细胞	调控血管稳定性并直接作用于神 经元	信号失衡:血管不稳定及浦肯野细胞树 突分支减少 ^[127]

注:CCL2(C-C motif chemokine ligand 2,C-C型趋化因子配体2);CXCL1(C-X-C motif chemokine ligand 1,C-X-C型趋化因子配体1);CXCL12(C-X-C motif chemokine ligand 12,C-X-C型趋化因子配体12);Netrin-1(网膜素-1);tPA(tissue plasminogen activator,组织纤溶酶原激活剂)。

氨酸介导的兴奋性毒性,导致神经元内钙超载及线粒体功能障碍^[145]。此外,活化的小胶质细胞经烟酰胺腺嘌呤二核苷酸磷酸(NADPH)氧化酶产生大量ROS,不仅可诱导脂质过氧化破坏细胞膜结构,还会损害线粒体电子传递链导致ATP合成受阻,从而加速神经元死亡进程^[146-148]。

除直接毒性作用外,胶质细胞的病理性功能重塑还会导致其原本生理功能受损。活化的小胶质细胞会错误吞噬健康突触,造成突触丢失及神经环路功能障碍^[149]。而在炎症刺激下,反应性星形胶质细胞谷氨酸摄取能力下降,其分泌BDNF、胶质细胞源性神经营养因子(glial cell line-derived neurotrophic

factor,GDNF)等神经营养因子的能力也显著受损,甚至还可分泌脂质毒性分子直接杀伤神经元^[150]。

尤为重要的是,在脑血管功能持续受损的情况下,神经炎症往往难以自限,易演变为自我强化的恶性循环。坏死的神经元释放高迁移率族蛋白B1(HMGB1)、线粒体DNA等DAMPs,经由Toll样受体(TLRs)进一步激活小胶质细胞^[151,152];而过度活化的胶质细胞释放基质金属蛋白酶(matrix metalloproteinase,MMPs),降解基底膜与紧密连接,进一步加重BBB破坏^[153]。由此,构成了“血管损伤-炎症激活-神经元死亡-炎症再放大-血管进一步损伤”的不可逆恶性循环,使神经免疫炎症进入持

续失控状态。

4 靶向脑血管的精准医学路径

靶向脑血管功能障碍干预CNS疾病已逐渐成为重要研究方向。相较于直接靶向神经元,血管靶向策略在转化层面具有独特优势:一方面,脑血管功能障碍常早于显著的神经元变性出现,为早期干预提供了关键时间窗口;另一方面,脑血管内皮细胞直接暴露于循环系统,药物更易到达作用靶点,部分规避了BBB对药物递送的限制。

4.1 基于影像学与体液生物标志物的早期诊断

发展无创且可定量的血管生物标志物对于识别CNS疾病早期变化具有重要意义。近年来,血管结构成像技术突破了传统空间分辨率的限制,使直径小于10 μm 的微血管结构及其血氧状态得以精细量化,为评估早期微血管重塑和功能改变提供了结构学依据^[154]。与此同时,基于伪连续动脉自旋标记(pseudo-continuous arterial spin labeling, pCASL)的大样本研究已建立起具有年龄和性别特异性的全脑脑血流参考图谱,为血流动力学状态提供了稳定的功能基线。这类以血管结构和血流功能为核心的影像学评估策略,不仅有助于区分早期病理性改变,也为在亚临床阶段筛选可能从血管靶向干预中获益的人群提供了更为可靠的分层工具^[155]。除影像学手段外,基于血液和脑脊液的体液生物标志物(如反映血管内皮损伤、微血管重塑或胶质细胞反应性的外周循环分子)在AD及其他神经退行性痴呆的早期诊断中也展现出巨大潜力^[156,157]。

4.2 基于多组学技术的靶点发现

近年来,单细胞与空间多组学技术的快速发展与应用,系统揭示了脑血管在疾病进程、区域分布以及疾病相关细胞亚型层面的多维异质性,为CNS疾病的精准靶向干预提供了新的分子基础。

首先,单细胞转录组学的发展使得在特定疾病阶段识别并靶向关键血管细胞类型成为可能,为疾病干预提供了更加精细的切入点。例如,在AD中,该技术揭示了血管相关细胞在疾病早期即发生功能变化,包括脉络丛上皮细胞出现屏障和线粒体功能相关基因下调,以及特定周细胞亚型表现出选择性脆弱性^[8,158]。近期研究将空间转录组学与单细胞测序技术相结合,在保留组织空间信息的前提下,系统解析了不同脑区内皮细胞与周细胞之间特异性的

配体-受体互作网络,从而阐明了脑区功能异质性的分子基础^[28]。鉴于多数CNS疾病具有明显的脑区特异性,这种对脑血管区域差异的精细刻画为筛选区域特异性靶点及设计精准药物递送策略提供了关键线索。此外,新兴的空间及单细胞蛋白质组技术的发展,使得病灶微环境中疾病相关蛋白的高分辨率定位成为可能^[159]。近来的代谢组学研究则揭示了疾病状态下NVU发生的代谢重编程特征,如能量代谢受损及关键代谢通路异常,为锁定血管相关代谢靶点提供了功能层面的依据^[160]。

总体而言,多组学技术的整合应用为筛选具有疾病相关性和区域特异性的血管靶点奠定了系统性基础。随着基因编辑技术和疾病模型的不断完善,基于分子分型的精细化调控正逐步具备机制验证与转化应用的可行性^[161-164]。

4.3 转化挑战与未来干预策略

尽管靶向脑血管功能障碍的治疗策略在机制研究层面取得了一定进展,其临床转化仍面临诸多挑战。首先,脑血管病变在不同脑区及疾病进展阶段呈现出显著异质性,使得干预时机的选择较为复杂。临床研究显示,针对A β 相关血管病变的他汀类药物以及RAGE抑制剂在已确诊AD患者中的疗效未能达到预期,提示当疾病进展至神经元广泛损伤的阶段,单纯针对血管异常的干预可能已难以逆转既定的神经退行性改变,也凸显了在更早病程阶段精准识别并干预血管病理的重要性^[165,166]。其次,NVU内部由多种细胞类型和信号通路共同构成高度复杂的调控网络,单一靶点的干预策略往往难以产生稳定疗效,甚至可能影响正常的血管生理功能。例如,非特异性的血管扩张剂(如钙通道阻滞剂)在AD治疗中的临床失败,可能与其干扰NVC的精细调控过程,或无法逆转既有的结构性血管损伤有关^[167]。此外,常用动物模型在脑血管结构特征、免疫反应模式以及疾病进展时间等方面与人类存在差异,这也在一定程度上制约了基础研究成果向临床的直接转化。

展望未来,研究重点应聚焦于构建一种融合宏观影像学信息与微观分子特征的精准诊疗模式。在患者分层方面,通过整合多组学分析与高分辨率影像学手段,从分子特征和血管功能双维度实现精细化分层,以识别可能从特定干预策略中获益的人群;在治疗策略层面,需要突破单一靶点干预的局限,探

索多靶点或联合治疗方案,以协同改善血管功能并提升整体疗效。在递送与干预技术方面,借助纳米递送系统、基因调控技术以及非侵入性干预手段的发展,提高药物递送效率并增强干预的靶向性与可控性。总体而言,靶向脑血管的治疗策略正向精准化与系统化发展,其临床应用前景取决于对疾病动态调控网络的解析,以及跨尺度多模态研究模式的整合与创新。

参考文献

- [1] GBD 2021 Forecasting Collaborators. Burden of disease scenarios for 204 countries and territories, 2022-2050: a forecasting analysis for the Global Burden of Disease Study 2021. *Lancet*, 2024, 403: 2204–56.
- [2] Mega Vascular Cognitive Impairment and Dementia (MEGAVID) consortium. A genome-wide association meta-analysis of all-cause and vascular dementia. *Alzheimers Dement*, 2024, 20: 5973–95.
- [3] Reid MM, Menon S, Liu H, et al. Human brain vascular multi-omics elucidates disease-risk associations. *Neuron*, 2025, 113: 3143–61.e5.
- [4] GBD 2021 Stroke Risk Factor Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet Neurol*, 2024, 23: 973–1003.
- [5] Kepp KP, Robakis NK, Høiland-Carlsen PF, et al. The amyloid cascade hypothesis: an updated critical review. *Brain*, 2023, 146: 3969–90.
- [6] Iadecola C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. *Neuron*, 2017, 96: 17–42.
- [7] Frackowiak RS, Pozzilli C, Legg NJ, et al. Regional cerebral oxygen supply and utilization in dementia. A clinical and physiological study with oxygen-15 and positron tomography. *Brain*, 1981, 104: 753–78.
- [8] Yang AC, Vest RT, Kern F, et al. A human brain vascular atlas reveals diverse mediators of Alzheimer's risk. *Nature*, 2022, 603: 885–92.
- [9] Pineda SS, Lee H, Ulloa-Navas MJ, et al. Single-cell dissection of the human motor and prefrontal cortices in ALS and FTL. *Cell*, 2024, 187: 1971–89.e16.
- [10] Garcia FJ, Heiman M. Molecular and cellular characteristics of cerebrovascular cell types and their contribution to neurodegenerative diseases. *Mol Neurodegener*, 2025, 20: 13.
- [11] Lo EH, Dalkara T, Moskowitz MA. Mechanisms, challenges and opportunities in stroke. *Nat Rev Neurosci*, 2003, 4: 399–415.
- [12] Schaeffer S, Iadecola C. Revisiting the neurovascular unit. *Nat Neurosci*, 2021, 24: 1198–209.
- [13] Divecha YA, Rampes S, Tromp S, et al. The microcirculation, the blood-brain barrier, and the neurovascular unit in health and Alzheimer disease: the aberrant pericyte is a central player. *Pharmacol Rev*, 2025, 77: 100052.
- [14] Tan C, Lu NN, Wang CK, et al. Endothelium-derived semaphorin 3G regulates hippocampal synaptic structure and plasticity via neuropilin-2/plexinA4. *Neuron*, 2019, 101: 920–37.e13.
- [15] Delgado AC, Ferrón SR, Vicente D, et al. Endothelial NT-3 delivered by vasculature and CSF promotes quiescence of subependymal neural stem cells through nitric oxide induction. *Neuron*, 2014, 83: 572–85.
- [16] Li S, Kumar TP, Joshee S, et al. Endothelial cell-derived GABA signaling modulates neuronal migration and postnatal behavior. *Cell Res*, 2018, 28: 221–48.
- [17] Li S, Haigh K, Haigh JJ, et al. Endothelial VEGF sculpts cortical cytoarchitecture. *J Neurosci*, 2013, 33: 14809–15.
- [18] He T, Zhang M, Qin J, et al. Endothelial PD-1 regulates vascular homeostasis and oligodendrogenesis during brain development. *Adv Sci (Weinh)*, 2025, 12: e2417410.
- [19] Wang W, Wang Y, Su L, et al. Endothelial cells mediated by STING regulate oligodendrogenesis and myelination during brain development. *Adv Sci (Weinh)*, 2024, 11: e2308508.
- [20] Kemp SS, Aguera KN, Cha B, et al. Defining endothelial cell-derived factors that promote pericyte recruitment and capillary network assembly. *Arterioscler Thromb Vasc Biol*, 2020, 40: 2632–48.
- [21] Stratman AN, Schwindt AE, Malotte KM, et al. Endothelial-derived PDGF-BB and HB-EGF coordinately regulate pericyte recruitment during vasculogenic tube assembly and stabilization. *Blood*, 2010, 116: 4720–30.
- [22] Hill SA, Bravo-Ferrer I, Čiulkinytė A, et al. Molecular profiling of brain endothelial cell to astrocyte endfoot communication in mouse and human. *Nat Commun*, 2025, 16: 9750.
- [23] Barnett SN, Cujba AM, Yang L, et al. An organotypic atlas of human vascular cells. *Nat Med*, 2024, 30: 3468–81.
- [24] Wälchli T, Ghobrial M, Schwab M, et al. Single-cell atlas of the human brain vasculature across development,

- adulthood and disease. *Nature*, 2024, 632: 603–13.
- [25] Mai-Morente S, Isasi E, Rafael A, et al. Pericyte pannexin1 controls cerebral capillary diameter and supports memory function. *Nat Commun*, 2025, 16: 6128.
- [26] Hartmann DA, Berthiaume AA, Grant RI, et al. Brain capillary pericytes exert a substantial but slow influence on blood flow. *Nat Neurosci*, 2021, 24: 633–45.
- [27] Eilken HM, Diéguez-Hurtado R, Schmidt I, et al. Pericytes regulate VEGF-induced endothelial sprouting through VEGFR1. *Nat Commun*, 2017, 8: 1574.
- [28] Pfau SJ, Langen UH, Fisher TM, et al. Characteristics of blood-brain barrier heterogeneity between brain regions revealed by profiling vascular and perivascular cells. *Nat Neurosci*, 2024, 27: 1892–903.
- [29] Li F, Lan Y, Wang Y, et al. Endothelial Smad4 maintains cerebrovascular integrity by activating N-cadherin through cooperation with Notch. *Dev Cell*, 2011, 20: 291–302.
- [30] Dias DO, Kim H, Holl D, et al. Reducing pericyte-derived scarring promotes recovery after spinal cord injury. *Cell*, 2018, 173: 153–65.e22.
- [31] Bernier LP, Hefendehl JK, Scott RW, et al. Brain pericytes and perivascular fibroblasts are stromal progenitors with dual functions in cerebrovascular regeneration after stroke. *Nat Neurosci*, 2025, 28: 517–35.
- [32] Institoris A, Vandal M, Peringod G, et al. Astrocytes amplify neurovascular coupling to sustained activation of neocortex in awake mice. *Nat Commun*, 2022, 13: 7872.
- [33] Mulligan SJ, MacVicar BA. Calcium transients in astrocyte endfeet cause cerebrovascular constrictions. *Nature*, 2004, 431: 195–9.
- [34] Magistretti PJ, Allaman I. Lactate in the brain: from metabolic end-product to signalling molecule. *Nat Rev Neurosci*, 2018, 19: 235–49.
- [35] Bojovic D, Dagostin A, Sullivan SJ, et al. Astrocyte gap junctions and K_{ir} channels contribute to K^+ buffering and regulate neuronal excitability. *Front Cell Neurosci*, 2025, 19: 1571218.
- [36] Salman MM, Kitchen P, Halsey A, et al. Emerging roles for dynamic aquaporin-4 subcellular relocalization in CNS water homeostasis. *Brain*, 2022, 145: 64–75.
- [37] Shi JH, Tang QL, Wang JH, et al. Pigment epithelium-derived factor deficiency impairs hippocampal glutamate homeostasis and cognitive function by downregulating astrocytic GLT-1. *Adv Sci (Weinh)*, 2025, 12: e00402.
- [38] Quan L, Uyeda A, Manabe I, et al. Astrocytic heterogeneous nuclear ribonucleoprotein U is involved in scar formation after spinal cord injury. *J Neuroinflammation*, 2025, 22: 28.
- [39] Fumagalli L, Nazlie Mohebiany A, Premereur J, et al. Microglia heterogeneity, modeling and cell-state annotation in development and neurodegeneration. *Nat Neurosci*, 2025, 28: 1381–92.
- [40] Jha RM, Rajasundaram D, Sneiderman C, et al. A single-cell atlas deconstructs heterogeneity across multiple models in murine traumatic brain injury and identifies novel cell-specific targets. *Neuron*, 2024, 112: 3069–88.e4.
- [41] Li H, Liu P, Zhang B, et al. Acute ischemia induces spatially and transcriptionally distinct microglial subclusters. *Genome Med*, 2023, 15: 109.
- [42] Favuzzi E, Huang S, Saldi GA, et al. GABA-receptive microglia selectively sculpt developing inhibitory circuits. *Cell*, 2021, 184: 4048–63.e32.
- [43] Császár E, Lénárt N, Cserép C, et al. Microglia modulate blood flow, neurovascular coupling, and hypoperfusion via purinergic actions. *J Exp Med*, 2022, 219: e20211071.
- [44] Bisht K, Okojie KA, Sharma K, et al. Capillary-associated microglia regulate vascular structure and function through PANX1-P2RY12 coupling in mice. *Nat Commun*, 2021, 12: 5289.
- [45] Lange C, Turrero Garcia M, Decimo I, et al. Relief of hypoxia by angiogenesis promotes neural stem cell differentiation by targeting glycolysis. *EMBO J*, 2016, 35: 924–41.
- [46] Zheng X, Boyer L, Jin M, et al. Metabolic reprogramming during neuronal differentiation from aerobic glycolysis to neuronal oxidative phosphorylation. *Elife*, 2016, 5: e13374.
- [47] Bovetti S, Hsieh YC, Bovolin P, et al. Blood vessels form a scaffold for neuroblast migration in the adult olfactory bulb. *J Neurosci*, 2007, 27: 5976–80.
- [48] Wang J, Tang Y, Zhang W, et al. Insulin-like growth factor-1 secreted by brain microvascular endothelial cells attenuates neuron injury upon ischemia. *FEBS J*, 2013, 280: 3658–68.
- [49] Licht T, Goshen I, Avital A, et al. Reversible modulations of neuronal plasticity by VEGF. *Proc Natl Acad Sci U S A*, 2011, 108: 5081–6.
- [50] Mango D, Nisticò R, Furlan R, et al. PDGF modulates synaptic excitability and short-latency afferent inhibition in multiple sclerosis. *Neurochem Res*, 2019, 44: 726–33.

- [51] Quirié A, Mor D, Méloux A, et al. Anxio-depressive phenotype and impaired memory in mice with a conditional knockout of brain-derived neurotrophic factor in endothelial cells. *Am J Physiol Cell Physiol*, 2025, 328: C303–14.
- [52] Friedman A, Prager O, Serlin Y, et al. Dynamic modulation of the blood-brain barrier in the healthy brain. *Nat Rev Neurosci*, 2025, 26: 749–64.
- [53] Zheng X, Ren B, Gao Y. Tight junction proteins related to blood-brain barrier and their regulatory signaling pathways in ischemic stroke. *Biomed Pharmacother*, 2023, 165: 115272.
- [54] Li W, Chen Z, Chin I, et al. The role of VE-cadherin in blood-brain barrier integrity under central nervous system pathological conditions. *Curr Neuropharmacol*, 2018, 16: 1375–84.
- [55] Chaves JCS, Dando SJ, White AR, et al. Blood-brain barrier transporters: an overview of function, dysfunction in Alzheimer's disease and strategies for treatment. *Biochim Biophys Acta Mol Basis Dis*, 2024, 1870: 166967.
- [56] Nguyen YTK, Ha HTT, Nguyen TH, et al. The role of SLC transporters for brain health and disease. *Cell Mol Life Sci*, 2021, 79: 20.
- [57] Baltira C, Aronica E, Elmquist WF, et al. The impact of ATP-binding cassette transporters in the diseased brain: context matters. *Cell Rep Med*, 2024, 5: 101609.
- [58] Andreone BJ, Chow BW, Tata A, et al. Blood-brain barrier permeability is regulated by lipid transport-dependent suppression of caveolae-mediated transcytosis. *Neuron*, 2017, 94: 581–94.e5.
- [59] Sadeghian H, Lacoste B, Qin T, et al. Spreading depolarizations trigger caveolin-1-dependent endothelial transcytosis. *Ann Neurol*, 2018, 84: 409–23.
- [60] Swissa E, Monsonogo U, Yang LT, et al. Cortical plasticity is associated with blood-brain barrier modulation. *Elife*, 2024, 12: RP89611.
- [61] Zhang SL, Lahens NF, Yue Z, et al. A circadian clock regulates efflux by the blood-brain barrier in mice and human cells. *Nat Commun*, 2021, 12: 617.
- [62] Zhang SL, Yue Z, Arnold DM, et al. A circadian clock in the blood-brain barrier regulates xenobiotic efflux. *Cell*, 2018, 173: 130–9.e10.
- [63] Chasseigneaux S, Cochois-Guégan V, Lecorgne L, et al. Fasting upregulates the monocarboxylate transporter MCT1 at the rat blood-brain barrier through PPAR δ activation. *Fluids Barriers CNS*, 2024, 21: 33.
- [64] Ito S, Yanai M, Yamaguchi S, et al. Regulation of tight-junction integrity by insulin in an in vitro model of human blood-brain barrier. *J Pharm Sci*, 2017, 106: 2599–605.
- [65] Maggioli E, McArthur S, Mauro C, et al. Estrogen protects the blood-brain barrier from inflammation-induced disruption and increased lymphocyte trafficking. *Brain Behav Immun*, 2016, 51: 212–22.
- [66] Atallah A, Mhaouty-Kodja S, Grange-Messent V. Chronic depletion of gonadal testosterone leads to blood-brain barrier dysfunction and inflammation in male mice. *J Cereb Blood Flow Metab*, 2017, 37: 3161–75.
- [67] Li Z, Wang B, Kan Z, et al. Progesterone increases circulating endothelial progenitor cells and induces neural regeneration after traumatic brain injury in aged rats. *J Neurotrauma*, 2012, 29: 343–53.
- [68] Vo TT, Jung WB, Jin T, et al. Somatostatin-expressing interneurons induce early NO-driven and late specific astrocyte-mediated vasodilation. *Nat Commun*, 2025, 16: 6606.
- [69] Zhang D, Ruan J, Peng S, et al. Synaptic-like transmission between neural axons and arteriolar smooth muscle cells drives cerebral neurovascular coupling. *Nat Neurosci*, 2024, 27: 232–48.
- [70] Krolak T, Kaplan L, Navas K, et al. Brain endothelial gap junction coupling enables rapid vasodilation propagation during neurovascular coupling. *Cell*, 2025, 188: 5003–19.e22.
- [71] Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β . *Sci Transl Med*, 2012, 4: 147ra111.
- [72] Chen K, Morizawa YM, Nuriel T, et al. Selective removal of astrocytic PERK protects against glymphatic impairment and decreases toxic aggregation of β -amyloid and tau. *Neuron*, 2025, 113: 2438–54.e6.
- [73] Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science*, 2013, 342: 373–7.
- [74] Hablitz LM, Plá V, Giannetto M, et al. Circadian control of brain glymphatic and lymphatic fluid flow. *Nat Commun*, 2020, 11: 4411.
- [75] Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. *Nat Rev Neurosci*, 2011, 12: 723–38.
- [76] Korte N, Nortley R, Attwell D. Cerebral blood flow decrease as an early pathological mechanism in Alzheimer's disease. *Acta Neuropathol*, 2020, 140: 793–810.
- [77] Shang S, Ye J, Wu J, et al. Early disturbance of

- dynamic synchronization and neurovascular coupling in cognitively normal Parkinson's disease. *J Cereb Blood Flow Metab*, 2022, 42: 1719–31.
- [78] Schuff N, Matsumoto S, Kmiecik J, et al. Cerebral blood flow in ischemic vascular dementia and Alzheimer's disease, measured by arterial spin-labeling magnetic resonance imaging. *Alzheimers Dement*, 2009, 5: 454–62.
- [79] Percie du Sert O, Unrau J, Gauthier CJ, et al. Cerebral blood flow in schizophrenia: a systematic review and meta-analysis of MRI-based studies. *Prog Neuropsychopharmacol Biol Psychiatry*, 2023, 121: 110669.
- [80] Jesmanas S, Milašauskienė E, Burkauskas J, et al. Cerebral blood flow and blood-brain barrier water exchange in major depressive disorder: evidence from diffusion-prepared arterial spin labelling MRI. *Brain Sci*, 2025, 16: 27.
- [81] Hall CN, Reynell C, Gesslein B, et al. Capillary pericytes regulate cerebral blood flow in health and disease. *Nature*, 2014, 508: 55–60.
- [82] Nanou E, Catterall WA. Calcium channels, synaptic plasticity, and neuropsychiatric disease. *Neuron*, 2018, 98: 466–81.
- [83] Huang X, Sun X, Wang Q, et al. Structural insights into the diverse actions of magnesium on NMDA receptors. *Neuron*, 2025, 113: 1006–18.e4.
- [84] Yan J, Bengtson CP, Buchthal B, et al. Coupling of NMDA receptors and TRPM4 guides discovery of unconventional neuroprotectants. *Science*, 2020, 370: eaay3302.
- [85] Wang JJ, Liu F, Yang F, et al. Disruption of auto-inhibition underlies conformational signaling of ASIC1a to induce neuronal necroptosis. *Nat Commun*, 2020, 11: 475.
- [86] Jia N, Ganesan D, Guan H, et al. Mitochondrial bioenergetics stimulates autophagy for pathological MAPT/Tau clearance in tauopathy neurons. *Autophagy*, 2025, 21: 54–79.
- [87] Myeku N, Clelland CL, Emrani S, et al. Tau-driven 26S proteasome impairment and cognitive dysfunction can be prevented early in disease by activating cAMP-PKA signaling. *Nat Med*, 2016, 22: 46–53.
- [88] Padamsey Z, Katsanevaki D, Dupuy N, et al. Neocortex saves energy by reducing coding precision during food scarcity. *Neuron*, 2022, 110: 280–96.e10.
- [89] Lu H, Diaz-Pier S, Lenz M, et al. The interplay between homeostatic synaptic scaling and homeostatic structural plasticity maintains the robust firing rate of neural networks. *Elife*, 2025, 12: RP88376.
- [90] Lau K, Kotzur R, Richter F. Blood-brain barrier alterations and their impact on Parkinson's disease pathogenesis and therapy. *Transl Neurodegener*, 2024, 13: 37.
- [91] Zierfuss B, Larochelle C, Prat A. Blood-brain barrier dysfunction in multiple sclerosis: causes, consequences, and potential effects of therapies. *Lancet Neurol*, 2024, 23: 95–109.
- [92] Duarte Lobo D, Nobre RJ, Oliveira Miranda C, et al. The blood-brain barrier is disrupted in Machado-Joseph disease/spinocerebellar ataxia type 3: evidence from transgenic mice and human post-mortem samples. *Acta Neuropathol Commun*, 2020, 8: 152.
- [93] Nation DA, Sweeney MD, Montagne A, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. *Nat Med*, 2019, 25: 270–6.
- [94] Montagne A, Nation DA, Sagare AP, et al. APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. *Nature*, 2020, 581: 71–6.
- [95] Matsuno H, Tsuchimine S, O'Hashi K, et al. Association between vascular endothelial growth factor-mediated blood-brain barrier dysfunction and stress-induced depression. *Mol Psychiatry*, 2022, 27: 3822–32.
- [96] Menard C, Pfau ML, Hodes GE, et al. Social stress induces neurovascular pathology promoting depression. *Nat Neurosci*, 2017, 20: 1752–60.
- [97] Chen ZL, Strickland S. Neuronal death in the hippocampus is promoted by plasmin-catalyzed degradation of laminin. *Cell*, 1997, 91: 917–25.
- [98] Mhatre M, Nguyen A, Kashani S, et al. Thrombin, a mediator of neurotoxicity and memory impairment. *Neurobiol Aging*, 2004, 25: 783–93.
- [99] Schachtrup C, Lu P, Jones LL, et al. Fibrinogen inhibits neurite outgrowth via $\beta 3$ integrin-mediated phosphorylation of the EGF receptor. *Proc Natl Acad Sci U S A*, 2007, 104: 11814–9.
- [100] Zhong Z, Ilieva H, Hallagan L, et al. Activated protein C therapy slows ALS-like disease in mice by transcriptionally inhibiting SOD1 in motor neurons and microglia cells. *J Clin Invest*, 2009, 119: 3437–49.
- [101] Kisler K, Nelson AR, Rege SV, et al. Pericyte degeneration leads to neurovascular uncoupling and limits oxygen supply to brain. *Nat Neurosci*, 2017, 20: 406–16.
- [102] Zhang X, Xu J, Fan Y, et al. Neutrophil extracellular traps aggravate neuronal apoptosis and neuroinflammation via

- neddylation after traumatic brain injury. *Theranostics*, 2025, 15: 7327–45.
- [103] Wilk CM, Cathomas F, Török O, et al. Circulating senescent myeloid cells infiltrate the brain and cause neurodegeneration in histiocytic disorders. *Immunity*, 2023, 56: 2790–802.e6.
- [104] Ahn JJ, Islam Y, Clarkson-Paredes C, et al. B cell depletion modulates glial responses and enhances blood vessel integrity in a model of multiple sclerosis. *Neurobiol Dis*, 2023, 187: 106290.
- [105] Rotstein M, Engelstad K, Yang H, et al. Glut1 deficiency: inheritance pattern determined by haploinsufficiency. *Ann Neurol*, 2010, 68: 955–8.
- [106] Guemez-Gamboa A, Nguyen LN, Yang H, et al. Inactivating mutations in MFSD2A, required for omega-3 fatty acid transport in brain, cause a lethal microcephaly syndrome. *Nat Genet*, 2015, 47: 809–13.
- [107] Ahmed HS. The multifaceted role of L-type amino acid transporter 1 at the blood-brain barrier: structural implications and therapeutic potential. *Mol Neurobiol*, 2025, 62: 3813–32.
- [108] Storck SE, Meister S, Nahrath J, et al. Endothelial LRP1 transports amyloid- β_{1-42} across the blood-brain barrier. *J Clin Invest*, 2016, 126: 123–36.
- [109] Osgood D, Miller MC, Messier AA, et al. Aging alters mRNA expression of amyloid transporter genes at the blood-brain barrier. *Neurobiol Aging*, 2017, 57: 178–85.
- [110] Bartels AL, Willemsen AT, Kortekaas R, et al. Decreased blood-brain barrier P-glycoprotein function in the progression of Parkinson's disease, PSP and MSA. *J Neural Transm (Vienna)*, 2008, 115: 1001–9.
- [111] Wang J, Cui Y, Yu Z, et al. Brain endothelial cells maintain lactate homeostasis and control adult hippocampal neurogenesis. *Cell Stem Cell*, 2019, 25: 754–67.e9.
- [112] Zhang W, Zhou Y, Wang J, et al. Glymphatic clearance function in patients with cerebral small vessel disease. *Neuroimage*, 2021, 238: 118257.
- [113] Yoon JH, Jin H, Kim HJ, et al. Nasopharyngeal lymphatic plexus is a hub for cerebrospinal fluid drainage. *Nature*, 2024, 625: 768–77.
- [114] Iturria-Medina Y, Sotero RC, Toussaint PJ, et al. Early role of vascular dysregulation on late-onset Alzheimer's disease based on multifactorial data-driven analysis. *Nat Commun*, 2016, 7: 11934.
- [115] Tărlungeanu DC, Deliu E, Dotter CP, et al. Impaired amino acid transport at the blood brain barrier is a cause of autism spectrum disorder. *Cell*, 2016, 167: 1481–94.e18.
- [116] Baronas VA, Yang RY, Morales LC, et al. Slc7a5 regulates Kv1.2 channels and modifies functional outcomes of epilepsy-linked channel mutations. *Nat Commun*, 2018, 9: 4417.
- [117] Mayerl S, Müller J, Bauer R, et al. Transporters MCT8 and OATP1C1 maintain murine brain thyroid hormone homeostasis. *J Clin Invest*, 2014, 124: 1987–99.
- [118] Zhi H, Wang Z, Zhu X, et al. Chronic liver injury decreases levels of cerebral carnitine and acetylcarnitine in rats partly due to the downregulation of organic cation transporters OCT1/2 and OCTN2 at the blood-brain barrier. *Drug Metab Dispos*, 2025, 53: 100072.
- [119] Deane R, Wu Z, Zlokovic BV. RAGE (yin) versus LRP (yang) balance regulates alzheimer amyloid beta-peptide clearance through transport across the blood-brain barrier. *Stroke*, 2004, 35: 2628–31.
- [120] Deane R, Du Yan S, Subramanyam RK, et al. RAGE mediates amyloid- β peptide transport across the blood-brain barrier and accumulation in brain. *Nat Med*, 2003, 9: 907–13.
- [121] Cirrito JR, Deane R, Fagan AM, et al. P-glycoprotein deficiency at the blood-brain barrier increases amyloid-beta deposition in an Alzheimer disease mouse model. *J Clin Invest*, 2005, 115: 3285–90.
- [122] Zhang C, Kwan P, Zuo Z, et al. The transport of antiepileptic drugs by P-glycoprotein. *Adv Drug Deliv Rev*, 2012, 64: 930–42.
- [123] Deguchi T, Isozaki K, Yousuke K, et al. Involvement of organic anion transporters in the efflux of uremic toxins across the blood-brain barrier. *J Neurochem*, 2006, 96: 1051–9.
- [124] Khanppanavar B, Maier J, Herborg F, et al. Structural basis of organic cation transporter-3 inhibition. *Nat Commun*, 2022, 13: 6714.
- [125] Zhang M, Su L, Wang W, et al. Endothelial cells regulated by RNF20 orchestrate the proliferation and differentiation of neural precursor cells during embryonic development. *Cell Rep*, 2022, 40: 111350.
- [126] Buchman AS, Yu L, Boyle PA, et al. Higher brain BDNF gene expression is associated with slower cognitive decline in older adults. *Neurology*, 2016, 86: 735–41.
- [127] Luck R, Karakatsani A, Shah B, et al. The angiopoietin-Tie2 pathway regulates Purkinje cell dendritic morphogenesis in a cell-autonomous manner. *Cell Rep*, 2021, 36: 109522.
- [128] Butovsky O, Jedrychowski MP, Moore CS, et al.

- Identification of a unique TGF- β -dependent molecular and functional signature in microglia. *Nat Neurosci*, 2014, 17: 131–43.
- [129] Pharaoh G, Owen D, Yeganeh A, et al. Disparate central and peripheral effects of circulating IGF-1 deficiency on tissue mitochondrial function. *Mol Neurobiol*, 2020, 57: 1317–31.
- [130] Aguiar-Oliveira MH, Boguszewski MCS, Rovaris DL, et al. Growth hormone and IGF-1 actions in the brain and neuropsychiatric diseases. *Physiology (Bethesda)*, 2026, 41: 0.
- [131] Terrando N, Monaco C, Ma D, et al. Tumor necrosis factor- α triggers a cytokine cascade yielding postoperative cognitive decline. *Proc Natl Acad Sci U S A*, 2010, 107: 20518–22.
- [132] Rossi S, Motta C, Studer V, et al. Interleukin-1 β causes excitotoxic neurodegeneration and multiple sclerosis disease progression by activating the apoptotic protein p53. *Mol Neurodegener*, 2014, 9: 56.
- [133] Rochfort KD, Collins LE, McLoughlin A, et al. Tumour necrosis factor- α -mediated disruption of cerebrovascular endothelial barrier integrity in vitro involves the production of proinflammatory interleukin-6. *J Neurochem*, 2016, 136: 564–72.
- [134] Matsumoto J, Dohgu S, Takata F, et al. TNF- α -sensitive brain pericytes activate microglia by releasing IL-6 through cooperation between I κ B-NF κ B and JAK-STAT3 pathways. *Brain Res*, 2018, 1692: 34–44.
- [135] Duan L, Zhang XD, Miao WY, et al. PDGFR β cells rapidly relay inflammatory signal from the circulatory system to neurons via chemokine CCL2. *Neuron*, 2018, 100: 183–200.e8.
- [136] Zhang K, Wang H, Xu M, et al. Role of MCP-1 and CCR2 in ethanol-induced neuroinflammation and neurodegeneration in the developing brain. *J Neuroinflammation*, 2018, 15: 197.
- [137] Grand Moursel L, Munting LP, van der Graaf LM, et al. TGF β pathway deregulation and abnormal phospho-SMAD2/3 staining in hereditary cerebral hemorrhage with amyloidosis-Dutch type. *Brain Pathol*, 2018, 28: 495–506.
- [138] Liu XX, Yang L, Shao LX, et al. Endothelial *Cdk5* deficit leads to the development of spontaneous epilepsy through CXCL1/CXCR2-mediated reactive astrogliosis. *J Exp Med*, 2020, 217: e20180992.
- [139] Li Y, Ru X, Xu Y, et al. Single-cell sequencing reveals intracranial microvasculature-derived CXCL12 promotes CD8⁺ T-cell infiltration and blood-brain barrier dysfunction after subarachnoid hemorrhage in mice. *J Neuroinflammation*, 2025, 22: 116.
- [140] Boyé K, Geraldo LH, Furtado J, et al. Endothelial Unc5B controls blood-brain barrier integrity. *Nat Commun*, 2022, 13: 1169.
- [141] Ji Y, Gao Q, Ma Y, et al. An MMP-9 exclusive neutralizing antibody attenuates blood-brain barrier breakdown in mice with stroke and reduces stroke patient-derived MMP-9 activity. *Pharmacol Res*, 2023, 190: 106720.
- [142] Henry VJ, Lecointre M, Laudénbach V, et al. High t-PA release by neonate brain microvascular endothelial cells under glutamate exposure affects neuronal fate. *Neurobiol Dis*, 2013, 50: 201–8.
- [143] Shi K, Zou M, Jia DM, et al. tPA mobilizes immune cells that exacerbate hemorrhagic transformation in stroke. *Circ Res*, 2021, 128: 62–75.
- [144] Gordon R, Anantharam V, Kanthasamy AG, et al. Proteolytic activation of proapoptotic kinase protein kinase C δ by tumor necrosis factor α death receptor signaling in dopaminergic neurons during neuroinflammation. *J Neuroinflammation*, 2012, 9: 82.
- [145] Viviani B, Bartesaghi S, Gardoni F, et al. Interleukin-1 β enhances NMDA receptor-mediated intracellular calcium increase through activation of the Src family of kinases. *J Neurosci*, 2003, 23: 8692–700.
- [146] Chouchani ET, Pell VR, Gaude E, et al. Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS. *Nature*, 2014, 515: 431–5.
- [147] Mills EL, Kelly B, Logan A, et al. Succinate dehydrogenase supports metabolic repurposing of mitochondria to drive inflammatory macrophages. *Cell*, 2016, 167: 457–70.e13.
- [148] Mendoza A, Patel P, Robichaux D, et al. Inhibition of the mPTP and lipid peroxidation is additively protective against I/R injury. *Circ Res*, 2024, 134: 1292–305.
- [149] Hong S, Beja-Glasser VF, Nfonoyim BM, et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. *Science*, 2016, 352: 712–6.
- [150] Guttenplan KA, Weigel MK, Prakash P, et al. Neurotoxic reactive astrocytes induce cell death via saturated lipids. *Nature*, 2021, 599: 102–7.
- [151] Fan H, Tang HB, Chen Z, et al. Inhibiting HMGB1-RAGE axis prevents pro-inflammatory macrophages/microglia polarization and affords neuroprotection after spinal cord injury. *J Neuroinflammation*, 2020, 17: 295.
- [152] Zhang M, Guo B, Zhang X, et al. IFP35, a novel

- DAMP, aggravates neuroinflammation following acute ischemic stroke via TLR4/NF- κ B/NLRP3 signaling. *J Neuroinflammation*, 2025, 22: 164.
- [153] Feng D, Zhou J, Liu H, et al. Astrocytic NDRG2-PPM1A interaction exacerbates blood-brain barrier disruption after subarachnoid hemorrhage. *Sci Adv*, 2022, 8: eabq2423.
- [154] Hohmann A, Zhang K, Mooshage CM, et al. Whole-brain vascular architecture mapping identifies region-specific microvascular profiles in vivo. *AJNR Am J Neuroradiol*, 2024, 45: 1346–54.
- [155] Meng Z, Ma Y, Zhang W, et al. Age- and sex-specific cerebral blood flow atlases for healthy brain across the lifespan. *Sci Data*, 2025, 12: 1169.
- [156] Wagner J, Degenhardt K, Veit M, et al. Medin co-aggregates with vascular amyloid- β in Alzheimer's disease. *Nature*, 2022, 612: 123–31.
- [157] Zetterberg H, Bendlin BB. Biofluid biomarkers in Alzheimer's disease and other neurodegenerative dementias. *Nature*, 2026, 650: 49–59.
- [158] Yan ZJ, Ye M, Li J, et al. Early transcriptional and cellular abnormalities in choroid plexus of a mouse model of Alzheimer's disease. *Mol Neurodegener*, 2025, 20: 62.
- [159] Mund A, Brunner AD, Mann M. Unbiased spatial proteomics with single-cell resolution in tissues. *Mol Cell*, 2022, 82: 2335–49.
- [160] Harshfield EL, Sands CJ, Tuladhar AM, et al. Metabolomic profiling in small vessel disease identifies multiple associations with disease severity. *Brain*, 2022, 145: 2461–71.
- [161] Lang Y, Wang Q, Li R, et al. Generation of the *Stmn2-Cre(ERT2)* mouse line targeting arterial endothelial cells. *J Genet Genomics*, 2024, 51: 1143–6.
- [162] Xu C, Li S, Cai Y, et al. Generation of *Slco1a4-Cre^{ERT2}-tdTomato* knock-in mice for specific cerebrovascular endothelial cell targeting. *Int J Mol Sci*, 2024, 25: 4666.
- [163] Song X, Cui Y, Wang Y, et al. Genome editing with AAV-BR1-CRISPR in postnatal mouse brain endothelial cells. *Int J Biol Sci*, 2022, 18: 652–60.
- [164] Li ZH, Wang J, Xu JP, et al. Recent advances in CRISPR-based genome editing technology and its applications in cardiovascular research. *Mil Med Res*, 2023, 10: 12.
- [165] Sano M, Bell KL, Galasko D, et al. A randomized, double-blind, placebo-controlled trial of simvastatin to treat Alzheimer disease. *Neurology*, 2011, 77: 556–63.
- [166] Galasko D, Bell J, Mancuso JY, et al. Clinical trial of an inhibitor of RAGE-A β interactions in Alzheimer disease. *Neurology*, 2014, 82: 1536–42.
- [167] Lawlor B, Segurado R, Kennelly S, et al. Nilvadipine in mild to moderate Alzheimer disease: a randomised controlled trial. *PLoS Med*, 2018, 15: e1002660.